Remarks

Claims 1-3, 5-9 and 12-102 are pending, however, only claims 1, 3, 5-9, 13-19, 21-24, 33 and 102 were examined. Applicants have canceled all pending claims in the amendments listed above and replaced them with new claims 103-109. No new matter is added. These new claims are based on previous claims 1, 13, 18, 21, 24 and 102 and are fully supported by the specification as filed. Applicants request reconsideration of the claims, rewritten to improve clarity and amended to cancel non-elected subject matter, at this time.

The Office has rejected the examined claims under 35 U.S.C. § 112, first paragraph on grounds of lack of enablement. The Office Action states that the specification enables a method using a library based on a native G protein Gα subunit carboxyl-terminal. Applicants would like to point out that the new independent claim, claim 103, recites a first library, the members of which have primary sequences based on the primary sequence of the eleven carboxyl-terminal amino acids of a native G protein Gα subunit that binds to the G protein binding domain of the GPCR under study by the screen (step a). The Office Action also asserts that the specification does not enable methods using "any or all types of a native Gα-subunit carboxyl terminal for the peptide library." Applicants do not understand why a peptide library based on a native G protein Gα subunit carboxy-terminal (generally) is enabled but "any or all types" of such a library are not. The two statements appear to be contradictory, especially since the native Gα subunits that are enabled are not specified.

All GPCR bind to one or more Gα subunit, as is known in the art. There exist a finite number of different Gα subunits, and these Gα subunits are classified in the art into four groups. The Office Action repeatedly refers to the genus of libraries as "numerous," "of huge scope," and similar language, however, the number of Gα subunits is not huge; the specification discloses all 16 unique Gα subunit types that were known to the inventors at the time of filing, and their carboxy terminal undecamers are listed in tables in the application. Should a new Gα subunit be

discovered, its carboxy terminus could be sequenced with routine work and a library could be constructed based on this sequence as well.

Furthermore, the GPCRs that bind to a particular native Gα subunit sequence are known or can easily be determined. Since the GPCR-Gα interaction is the same for each and every binding pair of GPCR and Gα, the screening for one GPCR-Gα library is analogous to the screening for any other binding pair. The Office has provided no reason why this would not be accepted by the skilled person and no reason why the Office doubts this, other than the repeated and misleading, unsupported statement that G proteins are "numerous."

Since the Gα subunits are finite in number and bind in an analogous manner to GPCRs, and since these Gα subunits are known in the art, Applicants submit that the guidance in the specification is more than sufficient to enable making a peptide library based on the primary sequence of the eleven carboxy-terminal amino acids of any native Gα subunit, whether specifically disclosed here or not. The art of preparing peptide libraries that contain variant sequences based on a known sequence is mature, and making such libraries is considered routine.

The Office Action asks Applicants to provide the "structure of the library" (page 3, line 9) to enable its screening. This "structure" includes the length of the variant peptide. Applicants do not understand what "variant peptide" is meant. A library as claimed here is made up of many (thousands or millions) of variant peptides, sometimes randomly generated, and in embodiments claimed here all based on the native sequence of one Gα subunit. Applicants have specified that the library is based on the primary sequence of a native G protein Gα subunit that binds to the GPCR being screened against, and now claims recite that the library members are based on the primary sequence of the eleven carboxy-terminal amino acids of a native Gα subunit.

The Office Action also remarks that the claims do not recite "the numerous native G-protein from which it [the variant peptide?] is based. The claims recite that the native Gα subunit is one which binds to the GPCR being screened against. Once one selects a GPCR for the screen, the Gα subunit selected is one that binds to said GPCR. See claim 1, step (a). Since the Gα subunits that bind a GPCR are known or easily determined and are <u>not</u> numerous (usually

only one or two per GPCR), the potential "numerous native G protein" does not exist. Applicants request clarification of what "it" refers to in the quoted phrase above and what the "numerous native G-protein" is.

While it is true that there are several GPCR and several G proteins, Applicants are not claiming all conceivable GPCR/Gα pairs to be used in the screen. The claim covers only a GPCR for screening with a library having sequences (*i.e.*, structure) based on a Gα peptide that binds to that GPCR. Therefore, the libraries which are recited for use in the screen are not of "huge scope" and are confined to a very small, easily discernable number of libraries based on the known structure of the one, two or several native Gα subunit carboxy-terminal sequences that bind to the selected GPCR. Persons of skill recognize a GPCR and know the Gα subunits which bind to it or how to use routine binding assays to test Gα subunits for binding. For example, if one chooses the human rhodopsin GPCR, PAR1, one would screen a library based on a Gα subunit that binds PAR1, *e.g.*, Gαi or Gαq, and not a Gα subunit that does not bind PAR1. If one selected a different GPCR, one would base the library on the Gα sequences that bind to that GPCR. Therefore, in the claimed method, the structures being screened are based on the structure of a known binder. These known binders are not a huge genus as the Office states.

The Office then asserts that "other distinguishing features" of the variant peptide are not disclosed. Applicants submit that the primary sequences of the claimed Gα undercamer carboxy termini on which the library is based in the claim are known in the art, disclosed in the specification or easily determined. Applicants do not understand what distinguishing features of the variant peptide (library member) the Office is referring to. Applicants have amended the claims to avoid the term "variant" which seems to have been a cause of some confusion.

The Office Action states that Applicants are required by law to provide guidance and reasonable assurance that "the exemplary SEQ ID NO:139" represents the "huge genus of the library as claimed." Applicants are confused as to whether the Office objects to the size of the library (number of members in the library) or the asserted large number of libraries. However, Applicants are not required by law to show that SEQ ID NO:139 represents the sequences upon

which libraries can be based. Applicants are required to provide sufficient guidance in the specification to enable a person of ordinary skill in the art to perform the two-screen method as claimed using a GPCR with a library based on the eleven carboxy terminal amino acids of a Gα subunit that binds to said GPCR. No skilled person would be unable to select a GPCR, select a Gα subunit that binds it, produce a library based on the carboxy terminal sequence of that Gα subunit and screen that library.

Applicants have provided the sequences of more than one Gα carboxy-terminal undecamer. SEQ ID NO:139 is one of the high affinity sequences (as selected in step c) during a screen using light-activated rhodopsin and a library based on a native Gαt sequence. See example 7. It is not proper in any case for the Office to ignore all examples but one and then require that this one library member from one example represent the claimed genus. Applicants submit that the several examples do provide sufficient guidance to enable a skilled person to choose a GPCR, choose a native Gα binder for that GPCR and make a library based on that native Gα binder.

The Office states that "the species of the recited G alpha is not controverted." Applicants do not understand this statement, however, it appears from the statement that the Office considers only one Gα to be recited in the main claim. The issue, as stated by the Office is "the huge scope of a library of variant peptides based on the primary sequence of a native G alpha subunit carboxyl terminal peptide." Here, it again appears that the Office is objecting to the fact that a library contains numerous compounds. This is true of all libraries, so it is difficult to understand why this is objectionable.

By way of explanation, the Office Action states that the specification does not disclose "the numerous G protein containing G alpha subunit carboxyl peptide sequences." It appears that the Office is criticizing the specification as failing to list the "numerous" Gα subunit carboxyl peptide sequences that contain G protein. There is no such things as a Gα subunit carboxyl-peptide sequence that contains G protein (a G protein-containing Gα sequence). Alternatively, the Office could be criticizing the specification as failing to list the "numerous" G proteins that

contain a Gα subunit carboxyl peptide sequence. However, all G proteins contain a Gα subunit carboxyl peptide sequence, and in fact the G protein is defined by which Gα subunit it has. Applicants have listed all 16 unique Gα subunit types and all Gα subunits that were known to them at the time of filing. Applicants request that the Office state plainly which specific objection is being made and whether disclosing all known members of a genus is not sufficient to disclose the genus.

The Office next criticizes the specification because it assertedly does not describe "the numerous variations of the different peptide sequences in each of the different G alpha subunit of a native G protein that results in a variant peptide library." This also is confusing. A library, by definition, is a collection of variant peptides. The library is not based on numerous different variant peptides - each library is based on one sequence of one Gα carboxyl terminal sequence and contains numerous peptides, each of which is a variant of that one sequence. Applicants request that the Office explain what variations of what sequences of the Gα subunits it asserts result in a library. Variations by themselves do not "result in a library." A library contains variant peptides but is not based on variations. The method used to make a library based on the primary sequence of a Gα peptide is explained in detail in the specification. Applicants request the Office review this at paragraphs 54-60, for example. Applicants note that the claims are rewritten here to attempt to advance prosecution recite that the first library is based on the primary sequence of the eleven carboxy-terminal amino acids of a native Gα subunit that binds to the GPCR. The library is based on a specific sequence of a very small number of polypeptides.

The Office then states that the total number of GPCR is "in itself a huge scope of receptors, let alone any G alpha that binds to it." The Office implies, without any proof, that the number of Gα subunits is even larger than the so-called "huge" scope of GPCR. This is not at all relevant to the question of enablement and is not true. All GPCR bind a Gα subunit in exactly the same way. There are only a small and finite number of Gα subunits, in contradiction to what the Office implies. Not only is the total number of Gα subunits small, but the number of Gα

subunits that bind to a particular GPCR is smaller. As explained above, one selects a GPCR (any GPCR) and then selects one of the Gα subunits that binds to it. Because all GPCR are identical with respect to their interaction with a Gα subunit and because the number of Gα subunits is finite, small and well-known in the art, the Office cannot reject these claims on lack of enablement without stating some specific and understandable reason that the numerous working examples using 8 different Gα subunit types (half of all those known) would not be sufficient to enable a skilled person to select any GPCR and a binding Gα and perform the same screen. Applicants request that the Office provide evidence that there are a huge number of undisclosed Gα subunits with which the skilled person is not familiar or cease making conclusions based on these ideas.

Applicants request that the Office supply some sort of support for its bare conclusion that GPCR are not enabled simply because there are a lot of them, when each and every GPCR binds to a G protein in the same manner, and binds to one or a few of a finite, small number of Gα carboxy termini. The only explanation given by the Office for the reason why an assertedly "huge scope" of GPCR is relevant to enablement of this screen is that some peptides in the library might not be expressed sufficiently. Not only are these two ideas not connected in any manner to each other, but neither is relevant to either the identity of GPCR in terms of G protein binding or the potential effectiveness of the screen.

It is virtually guaranteed that some peptides in the library will not bind to a particular GPCR. The point of screening a library is not to prove that all members of the library bind, but to identify the few peptides that do bind. A screen does not fail simply because all peptides do not bind. Whether a peptide does not get expressed sufficiently also is not relevant to the screen. To reject a claim to a binding assay unless all samples tested bind is ludicrous. An assay must be specific to be useful; therefore, some examples (library members) will fail to bind. A library is a collection of samples to be tested. In this case, the collection of samples are all of a related structure because they are based on the same Gα sequence. That does not mean that all library members should be expected to bind. And it does not even relate to the receptor tested.

The Office states on page 5 of the Office Action that "a single native protein Gα covers numerous subsets *e.g.*, G alpha t, i ...." Applicants do not understand why the Office repeatedly refers to Gα "subsets" or "numerous" Gα. Applicants request that the Office explain what "numerous" Gα there are which are not already specifically disclosed here. The skilled person would have known that for each GPCR there are only one or a few binding Gα subunits. He would not be forced to guess from "numerous variations" of Gα. There are only a small, finite number of Gα. See, for example, Table II. The skilled person knows what Gα binds a specific GPCR, and if he does not know, the routine assays to determine are discussed in the art and in the specification.

The Office then refers to "variations" for each Gα "to form a library." How a library is formed based on a single Gα sequence is described in detail in the specification. The Office seems to be unfairly requiring Applicants to provide the sequence of each individual library member. If this is so, Applicants request the Office state so plainly. The methods of making libraries and the sequences that can be present in the resulting library are described in terms a skilled person understands, in the specification. Applicants request that the Office take the specifications' disclosures into account rather than repeating that "variations" are not provided. Applicants request the Office clearly explain what variations should be provided, however, the claims have been amended as discussed above to avoid the term "variant" which has apparently caused confusion. (Office Action, p. 5, line 10-11). Libraries are not based on undisclosed variations of Gα subunits - the library of the claims is based on <u>one</u> Gα subunit undecamer carboxy terminal native sequence in the claims here amended to advance prosecution. The artisan needs to know only one GPCR (any GPCR of choice) and one Gα subunit which binds to this GPCR. He does not need to know specifically all possible variations of all Gα subunits, which is what the Office seems to require. The library is based on <u>one</u> sequence only for each screen and contains sequences of similar sequence to the native sequence which would be easily understood and made by the skilled person.

In the final paragraph of page 5, the Office again chooses two of the many examples of the specification and denies that they represent all GPCR. It is not proper to ignore the other examples. Furthermore, since all GPCR are by definition analogous, the examples of the specification are representative of all GPCR.

The Office then refers to "numerous undefined compounds." Applicants request that the Examiner review the amended claims and state what these undefined compounds are so that Applicants can address each in turn.

The Action states that Gαt "in and of itself" covers numerous variations of each amino acid based on the "parent alpha subunit." As explained above, Gαt is a single, unique polypeptide. Its 11-mer carboxy terminus is provided in the specification in SEQ ID NO:15 in Table II. There is no "parent alpha subunit" of Gαt. Gαt is the alpha subunit. The primary sequence of the eleven carboxy-terminal amino acids of the native G protein Gα subunit Gαt is IKENLKDCGLF. Applicants have described in detail in the specification how to make an appropriate library using the example in Table I, page 22, and others but submit that the Office has given no reason why any random peptide library could not be screened using this method or why it would be necessary to know the precise sequence of each of the billions of library members before a screen is enabled. Until a reason can be provided by the Office, Applicants submit rejections based on this are improper.

The Office Action then discusses the second screen of the claim, which involves testing a second library for binding to the same binding region of the GPCR. The primary objection to the specification disclosures seems to be that the composition of this second library is not specifically disclosed. However, the Office states: "More importantly, the small molecules found to compete with the library of G alpha subunit for the method to work." This statement contains no verb. Applicants therefore are unclear as to the meaning.

First, the second library members (*e.g.*, small molecules) do not compete with the "library of G alpha subunits" at any step of the screen. The second screen is a screen of a library in competition with a peptide which was identified in the first screen step. There are never two

competing libraries. Second, whether the method "works" is not determined by whether a library member is identified as a binder. Even if no second library member birds, the assay has still worked. Therefore, small molecules found to compete are not required. The method is an assay. An assay is a test to determine the presence or absence of some phenomenon. If the phenomenon is not present, the assay determines this. If the phenomenon is present, the assay determines this as well. Either way, the assay has worked. In drug discovery, an art in which this two-step assay can be useful, it is considered routine to screen multiple libraries and considered routine to screen very large numbers of compounds before finding a compound that binds well and eventually is identified as a useful drug compound. The Office has misunderstood how the invention works. The second screen step is intended to be a screen of any library in a competitive binding assay with a peptide which resulted from the first screen. Binding assays are known and competitive binding assays are known. Any compound may be subjected to an assay for binding. If a compound does not bind, this does not signal failure of the assay – it only means that the assay determined no binding occurred.

The previous Office Action stated on page 15, lines 9-11, that incorporating the sequences of Table III of the specification to form a variant peptide library would obviate the rejection under §112. Applicants had attempted to do so. Applicants assumed that the Office was stating that libraries based on the sequences specifically disclosed in the specification were enabled. However, the Office now asks how these sequences "form" a library with the other sequences of tables I and VI. It therefore is not clear what the Office Action was requesting. Applicants request that the Office state definitively whether the Office considers only libraries which contain the sequences of Table III to be enabled or whether the Office considers only libraries which are based on the sequences of Table III to be enabled.

If it is the former (only the peptides of Table III can be screened) then Applicants do not understand the question. Is the Office asking how to group the sequences recited in Table III with the sequences of Table I and the sequences of Table VI into one collection? If one wished to group these compounds together in one collection, one simply would place them together,

literally or figuratively, and refer to them as a library. Applicants intended to claim the sequences of Gα subunits disclosed in Tables II-VI in terms of primary sequences of native Gα subunits on which a library could be based, and not as library members. A library is a collection of compounds. Generally speaking a library can contain any compounds. The libraries which are intended to be referred to in claim 103, step (a) are collections of compounds that have sequences which are variants of the one Gα subunit peptide on which they are based. These types of libraries are known to those of skill and are explained in the specification.

The Office refers to the library of Table I and the library of Table VI. Neither of these Tables is disclosed to contain a library. Table I is an example of an oligonucleotide to construct a library based on SEQ ID NO:13. It is not a library itself. Table II is a list of exemplary Gα subunit peptides and their corresponding DNA sequences which can be used instead of the DNA encoding SEQ ID NO:13 in the construct of Table I. It also is not a library. It is a list of some sequences on which one can base a library. Table III is a list of sequences useful for constructing a library. It also is not a library. Table IV is a list of some members of a Gαq library which exemplify the types of sequences which can be library members. It is a portion of a library. Table V is a list of some members of the Gαq library discussed immediately above. This list exemplifies the selection process of the screens in some of the inventive embodiment. Table VI is a list of some exemplary C-terminal minigene peptides and is meant to show 11-mers having a C-terminal MG, for a total of 13 amino acids, which show part of the method for making minigene vectors for peptide libraries. None of Tables I-VI is a library per se. Applicants would like to refer the Office to Example I, which shows one way to make a peptide library, and paragraphs 54-58, which discuss other libraries and preferred libraries.

Moreover, it makes absolutely no sense whatsoever to screen the compounds of Table III in the method claimed. These are native Gα subunit sequences for the most part, and therefore it would not be possible to identify among them a compound that binds the GPCR with higher affinity than the (competitive) native Gα subunit sequence which already is known to bind. Applicants request withdrawal of this rejection.

Claims 1, 3, 5-9, 13-19, 21-24, 33 and 102 are rejected for lack of written description. Applicants refer the Office to original claims 15 and 17, which claims recite a competitive binding assay characterized by co-incubation of peptide library members with the GPCR binding peptide. Description in the examples also discloses a competitive binding assay performed in the presence of the native Gα peptide. This also is discussed in paragraph 61, for example. Thus, the quoted phrase in page 7 of the Office Action is not a new limitation. Applicants request the rejection be withdrawn.

The pending claims are rejected as indefinite under 35 U.S.C. §112, second paragraph. The claims have been amended for clarity. Applicants request reconsideration and withdrawal of this rejection.

Claims 1, 3, 5-9, 13-19, 21-24, 33 and 102 are rejected as obvious over Fowlkes and Gilchrist of record. No new reasons are advanced. The Action indicates that it is well known that "the only goal of screening ... is to obtain ... higher affinity binders." No art is cited for this conclusion, which is in direct contradiction to what is taught in the art cited by the examiner. Moreover, this statement is not relevant to the rejection of claims as obvious. The Office states that while it is true that the Fowlkes peptide "interactions will be of considerably lower affinity." This is taken out of context because it is possible to drive the interaction by using a "vast excess" of peptide to "search for effects." The present invention does not require a vast excess to "search for effects" because it is a different method which identifies high affinity binders in contradistinction to Fowlkes. The Office is required to cite art which teaches or fairly suggests all elements of the claim, however here the Office admits the Fowlkes peptides do not meet the claims but asserts it is not relevant because the inferior method also could be used. A different method which requires a vast excess of peptide is not the same as teaching as what is claimed.

The Office Action also states that it would have been obvious to screen for higher affinity compounds. Even if the skilled person were motivated to screen for higher affinity compounds, there is nothing in the art which would suggest the method which is claimed. The cited art only provides a vague wish in the art to find lead compounds – it does not teach or suggest what is

claimed and the Office Action does not even point to any specific suggestions in the art which guide the artisan to the claims here. The only cited art is admittedly different assays and an unsupported conclusion that since all artisans want better compounds they naturally would achieve them – all without any specific suggestions or motivations in the art or how to do this.

The Office here has missed the entire point of this invention. The invention comprises an assay which can be used to test large members of compounds, any compounds, and can identify those compounds among the group tested which are very high binders to the intracellular, G protein-binding site on a GPCR. The Fowlkes assay cannot do this and does not even suggest how. Neither does the Gilchrist reference teach or suggest all elements of this assay. Together, these references still do not teach or suggest all elements. The Office Action apparently concludes that since it would be obvious to do better, that one simply could use the Fowlkes assay on the Gilchrist binding site and it would achieve the claim. All this based on the unsupported idea that all screens are nothing more than a fishing expedition for binding compounds. The claims recite specific methods for which the examiner has not cited any art which even suggests the steps.

It is not proper to reject a method claim merely because the Office believes that all screens are the same, regardless of the steps claimed. Applicants request that the Office explain what steps of Fowlkes teach or suggest the elements of the claim. The only explanation for the rejection now is that Fowlkes and the claimed method both "hope" that some members of the library will bind with higher affinity than the native sequence. However, the claim is directed to a two-step method which is not taught in Fowlkes and not suggested by Fowlkes. In summary, Applicants respectfully request that the Office point to specific teachings in the cited art which disclose or suggest the claim elements rather than continue to reject the claims based on an asserted similarity among all screens. The Office is required to meet the "all-elements test" and to show specific motivation to perform the method steps of the claims, as well as a reasonable expectation of success to make out a prima facie case of obviousness. If the Office cannot

produce this evidence of obviousness based on specific teachings in the art and not in unsupported beliefs, the rejection must be withdrawn.

Furthermore, as long as the Office cannot provide a clear and understandable reason why the claims are enabled for methods using a library "based from" a native G protein Gα-subunit carboxyl terminal and only a specific peptide library "for the candidate compounds," Applicants will not be able to make progress in this application. Applicants had attempted to modify the claims to comply with the Examiner's suggestions, in order to make progress, without disclaiming any of the canceled subject matter. However, although the Action states that methods "based from" a native Gα carboxy terminal are enabled, the comments imply these methods are not enabled because one cannot proceed with screening when no "structure of the peptide" except what it is based on is provided. These two ideas stated at pages 2-3 of the Office Action are directly contradictory and have resulted in confusion especially given that the peptide referred to and what structure would be required is not clearly stated. Other confusing and contradictory statements are discussed above, with respect to the disclosures of the specification and the art.

Applicants have made a sincere attempt to streamline the application for the benefit of the Office here and request a sincere reconsideration of the claims, with a reasoned explanation in clear language as to deficiencies which remain, if any, in the opinion of the Office.

In summary, Applicants request that the Office refer to the specification for its discussion and explanation as to how G protein signaling operates, the finite family of Gα subunits (totaling 16 unique types at the time of filing) which define a G protein type, library construction (showing how they are made based on primary structure, regardless of length), library types which may be screened in the second step and the like. The disclosures have been pointed out in numerous previous discussions in previous responses. Applicants also request that the Office review the claims and compare the elements of the claims to the art teachings and what they fairly suggest.

If the Examiner believes that a telephonic or personal interview would be of benefit, Applicants invite the Examiner to telephone the undersigned. Especially in light of her statement

on page 11 of the Action that the elected species is free of prior art, Applicants believe that an allowable claim directed at least to this subject matter can be drafted. Applicants would like to point out that new claim 109 recites the elected species SEQ ID NO:38 as the Gα subunit.

<table>
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